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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Anthony J. McHugh, et al.

Serial No. 09/733,640

Filing Date: December 8, 2000

For Crystallizable/Non-Crystallizable Composites

Examiner Sharmila S. Gollamudi

Group Art Unit No. 1616

TRANSMITTAL OF APPELLANTS' BRIEF ON APPEAL

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Dear Sir:

Appellants submit the following:

1. Credit Card Payment ($165 for Brief and $475 for three-month extension).
2. Appellants' Brief on Appeal under 37 C.F.R. § 1.192 in support of the Notice of Appeal received by the USPTO on February 20, 2004, including Appendices A and B (in triplicate).
3. Three Month Extension of Time (in duplicate).
4. Change of Correspondence Address

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Respectfully submitted,

Paul E. Rauch, Ph.D.,
Registration No. 38,591

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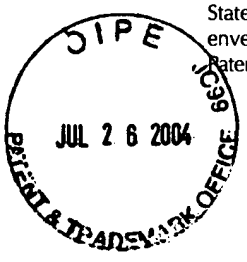

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Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor/s:	McHugh, et al.
Serial No.:	09/733,640
Filing Date:	December 8, 2000
Title:	Crystallizable/non-crystallizable Polymer Composites
Examiner:	Gollamudi
Group Art Unit:	3763

M.S. - Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICANT'S BRIEF IN SUPPORT OF THE APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

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I. REAL PARTY IN INTEREST

The real party in interest is the Board of Trustees of the University of Illinois.

II. RELATED APPEALS AND INTERFERENCES

There are no other related appeals or interferences.

III. STATUS OF CLAIMS

Original claims 9-16, 20-33, 35-37, and 39-47 have been cancelled. All of the pending claims, originally filed claims 1-8, 17-19, 34, and 38, and previously added claims 48-59, have been finally rejected and are appealed.

IV. STATUS OF AMENDMENTS

The final rejection was mailed on November 14, 2003 (Paper No. 17). On June 18, 2004, Applicants filed an amendment to the claims under 37 C.F.R. § 1.116 to correct minor typographical errors in the claim numbering. No amendments were filed subsequent to June 18, 2004.

V. SUMMARY OF THE INVENTION

The present invention includes a combination of a crystallizable polymer and an amorphous polymer.[1] The amorphous polymer may provide a slow release of an entrained bioactive agent at a constant or nearly constant rate, often referred to as zero-order kinetics. (Application, Page 1, Lines 13-15; Page 19, Lines 21-24). The crystallizable polymer may provide rapid release of an entrained bioactive agent during crystallization, referred to as non-zero-order kinetics. (Application, Page 19, Lines 5-6).

The ratio of the crystallizable polymer to the amorphous polymer in a specific composition may be altered to provide the desired profile of non-zero-order and zero-order release for the bioactive agent. (Application, Page 3, Lines 28-29). For example, the ratio chosen may provide a rapid release at the desired time point provided by the crystallizable polymer in combination with a substantially longer, but lower concentration, release provided by the amorphous polymer. (Application, Page 19, Lines 20-30).

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[1] A "crystallizable polymer" assumes a "semi-crystalline" order when crystallized. All polymers capable of adopting a semi-crystalline order are crystallizable. Amorphous polymers cannot assume a semi-crystalline order and are not crystallizable.

VI. ISSUES

The issues to be decided on this appeal are as follows:

Whether claims 1-3, 5-6, 34, 38-49, 51, 52, and 59 are anticipated under 35 U.S.C. § 102(b) over *McHugh* et al (*McHugh*). (Mat. Res. Soc. Symp. Proc. 550:41-46 1999).

Whether claims 1-3, 5-6, 8, 34, 38, 48-49, 51-52, 54, and 58-59 are anticipated under 35 U.S.C. § 102(b) over *Brodbeck* et al (*Brodbeck*). (Journal of Controlled Release 62 (1999) 333-44).

Whether claims 1-3, 5-6, 34, 38, 48-49, 51-52, and 58-59 are anticipated under 35 U.S.C. § 102(a) over *Graham* et al (*Graham*). (Journal of Controlled Release 58 (1999) 233-45).

Whether claims 1-3, 5-7, 17, 34, 38, 48, 49, 51-53, 55, and 59 are anticipated under 35 U.S.C. § 102(e) over U.S. Patent 6,432,438 to *Shukla* (*Shukla*).

Whether claims 19 and 56 are obvious under 35 U.S.C. § 103(a) over *Shukla* alone or in view of WO 00/19837 to *Weisheng* (*Weisheng*).

Whether claims 4, 8, 19, 50, 54, and 57 are obvious under 35 U.S.C. § 103(a) over *Shukla* in view of U.S. Patent 6,130,200 to *Brodbeck* (*Brodbeck* '200).

Whether claims 4, 7, 19, 53, and 57 are obvious under 35 U.S.C. § 103(a) over *McHugh* or *Brodbeck* or *Graham* in view of the *Brodbeck* '200 patent.

VII. GROUPING OF CLAIMS

The claims of each group do not stand or fall together. Each claim is independently patentable. Arguments as to the independent patentability of each claim are presented below in Section C of the Argument.

VIII. ARGUMENT

The Examiner has failed to consider all the limitations of the claims. In particular, the claims include a crystallizable polymer and an amorphous polymer. The Examiner has ignored these terms, apparently due to two fundamental misunderstandings.

Claim 1, the only independent claim in the present application, specifies the inclusion of a crystallizable polymer and an amorphous polymer. Crystallizable polymers may attain semi-crystalline or crystalline states. Whether a polymer is crystallizable may be determined by the presence of an endothermic transition as measured by differential scanning calorimetry (DSC) analysis; this transition occurs at the melting temperature, the temperature above which the crystalline domains, or crystallites, in the polymer become disordered. (Application, Page 4, Lines 3-10). Once a crystallizable polymer has

crystallized, it also will display a pattern of rings, spots, or arcs when analyzed by X-ray diffraction techniques. (Application, Page 4, Lines 10-12). In contrast, an amorphous polymer refers to a polymer which is not capable of organizing into ordered morphologies, and is characterized by the absence of a melting temperature (i.e. endothermic transition) in DSC analysis and by the absence of a crystalline X-ray diffraction pattern. (Application, Page 4, Lines 13-15).

Whether a specific polymer is amorphous or crystallizable is an intrinsic physical property of the specific polymer, and depends on its atomic composition and molecular arrangement and is unrelated to its surroundings or use. The molecular structure of a specific polymer can either attain a semi-crystalline or crystalline state, or it cannot.

An intrinsic physical property is inherent and inseparable from a specific material, and therefore the Examiner must consider whether polymers described in the cited references are crystallizable when the pending claims are examined. In re Papesch, 315 F.2d 381, 391; 137 USPQ 43, 51 (CCPA 1963) (holding that "from the standpoint of patent law, a compound and all of its properties are inseparable"). (MPEP § 2141.02).

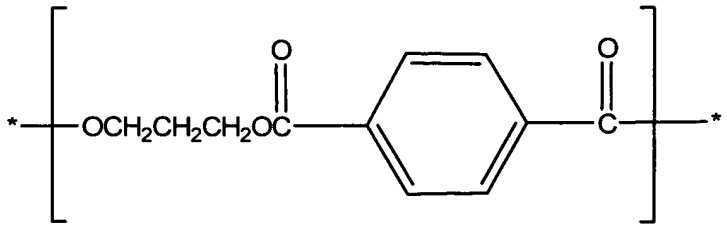
First, the Examiner believes that the term crystallizable is somehow related to the use of the polymer. This misconception is demonstrated in the Office Action of July 2, 2002 by the statement "that claim 1 recites a "crystallizable polymer" and not crystallized polymer, which is an intended use

limitation." (Paper No. 9, Office Action, Page 2). Whether a polymer is used as an adhesive, plastic wrap, or car part does not determine whether it is crystallizable or amorphous, since this is an intrinsic property of the polymer.

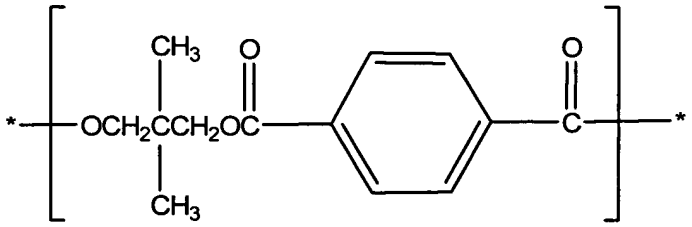
Second, the Examiner has confused terms used for classes of polymers, believing that they designate a specific species of polymer. This misconception is demonstrated on page 3 of the office action, which states that "claim [*15*] claims polyester as the crystallizable polymer and claim 17 claims polyester as the amorphous polymer and the claims do not distinguish the two polymers since crystallizable implies the ability to crystallize." (Paper No. 9, Office Action, Page 3). In fact, the term "polyester" designates a class of polymers, some of which are crystallizable, while others are amorphous. (See, for example, the Application, Page 5, Lines 6-18, which lists families of polyesters which are crystallizable and families of polyesters which are amorphous). Failing to recognize that class designations, such as polyester, include many different polymers with different physical properties, the Examiner erroneously assumes that all polymers within each class are either all crystallizable or all amorphous.

In fact, the term crystallizable clearly differentiates between the two distinct types of polyester. For example, in Stevens, Polymer Chemistry an Introduction, 3rd ed., pp.82-83 (1999), three different polyesters (A, B, and C) are

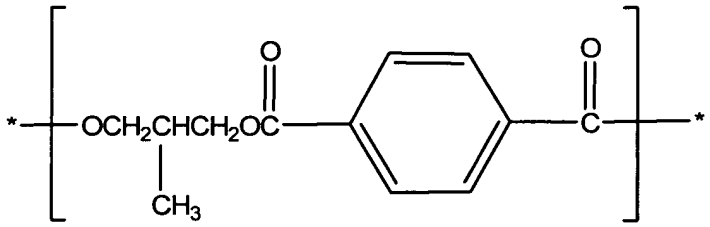
described, each having a different molecular structure (the structures of these polymers are shown below).



Polyester A (crystallizable)



Polyester B (crystallizable)



Polyester C (non-crystallizable)

While A, B, and C are all polyesters, polyesters having the structures A and B are crystallizable, while the polyester having structure C is not. Thus, polyesters A and B are crystallizable polymers, while polyester C is amorphous. This example, as well as the specification of the present application, makes it very clear that not all polymers can crystallize and that the term crystallizable represents a physical property that may be used to differentiate polymers.

The Examiner must consider and give weight to both the term "crystallizable" and "amorphous." Alone, the class name of a polymer provides no guidance as to whether the polymer being referred to is crystallizable or amorphous. Simply specifying that polyester, for example, is used in a composition provides no teaching as to whether the polymer selected is crystallizable or amorphous. Thus, the mere recitation of the name of a class of polymers in a reference is insufficient to determine if the polymer described is crystallizable or amorphous.

A. The Examiner's Failure to Appreciate the Terms "Crystallizable" and "Amorphous" as an Intrinsic Physical Property of a Polymer Has Resulted in Erroneous Rejections Under 35 U.S.C. § 102 Over *McHugh, Brodbeck,* and *Graham.*

Once the terms crystallizable and amorphous are given proper interpretation, the anticipation rejections under *McHugh*, *Brodbeck*, and *Graham* must be withdrawn because none of these references teach a crystallizable polymer in combination with an amorphous polymer. For a reference to be anticipatory, it must teach every element of the claimed invention. Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747, 3 USPQ2d 1766 (Fed. Cir. 1987), cert. denied, 484 U.S. 1007 (1988) ("Anticipation under 35 U.S.C. Section 102 requires the presence

in a single prior art disclosure of each and every element of a claimed invention."). (MPEP § 2131.01).

McHugh, *Brodbeck*, and *Graham* teach implantable gels for drug delivery using amorphous PLGA and various additives to modify the delivery profile of the drug. (*McHugh*, Page 42; *Brodbeck*, Page 334; *Graham*, Page 236). Without any factual basis, the Examiner asserts that the PLGA used in these references is crystallizable.[2] (Paper No. 17, Office Action, Page 2, 3). In fact, the Examiner's assertion is incorrect because the PLGA Resomer 502 as used in the references is an intrinsically amorphous polymer that cannot attain a semi-crystalline or crystalline form.[3]

The anticipation rejections over *McHugh*, *Brodbeck*, and *Graham* must be withdrawn because they lack any factual basis; they are based on assumptions that are demonstrably wrong.[4] *McHugh*, *Brodbeck*, and *Graham* fail to teach or suggest the inclusion of a biodegradable crystallizable polymer. Instead, the references teach amorphous polymers that undergo phase inversion to release a

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[2] It appears that the Examiner confused phase inversion with crystallization. These concepts are not related.

[3] Poly(D,L-lactide-co-glycolide) 50:50 is an intrinsically amorphous (glassy) polymer. Therefore, no crystallinity and hence no different crystal structures can occur. (*See* Section C.1.2.5.2, Documentation on Poly(D,L-lactide-co-glycolide) in Appendix B).

[4] The Examiner appears to believe that the mere appearance of the name of any polymer class that may include crystallizable members, such as PLGA, anticipates the "biodegradable crystallizable polymer" element as required by the present claims. As explained above with regard to polyesters, and previously during a September 13, 2002 examiner interview, this is wrong. The name given a class of polymers has no relation to and provides no guidance as to whether one or more members of that polymer class can or cannot crystallize.

drug. Thus, the Examiner has failed to find these claim elements in the references, because the assumptions underlying the rejections are incorrect.

B. The Infinite List of Polymer Combinations Taught in *Shukla* Cannot Anticipate the Specific Combination of a Crystallizable Polymer with an Amorphous Polymer.

Claim 1 includes a biodegradable crystallizable polymer and a biodegradable amorphous polymer. *Shukla* is the only reference cited by the Examiner under 35 U.S.C. § 102 that mentions crystallinity. However, the mere mention that a crystallizable polymer may be included, in a reference describing the alternative inclusion of many other polymers having a multitude of varying physical properties, is insufficient for anticipation. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) ("The identical invention must be shown in as complete detail as is contained in the...claim."). Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 780, 227 USPQ 773 (Fed. Cir. 1985) ("[A]nticipation under Section 102 can be found only when the reference discloses exactly what is claimed. . . ."). (MPEP § 2131.01, 2131.03).

Shukla describes a biodegradable vehicle and filler. There is no specific description of a mixture of crystallizable and amorphous polymers. In fact, *Shukla* only mentions crystallinity in column 3, column 9, and in example 29. The paragraph addressing crystallinity from column 3 is reproduced below:

> According to the present invention, the term polymer includes oligomer, copolymer and terpolymer. **Biodegradable polymers** are used in this invention because they form vehicles that can degrade in vivo into non-toxic degradation products. Moreover, these polymers **are available in varying physicochemical properties including varying hydrophilicity and hydrophobicity, varying molecular weights, varying crystallinity and amorphous states and varying copolymer ratios**. Tailoring either the degradation kinetics of the biodegradable vehicle or the release characteristics of the BAS from the BAS-loaded biodegradable vehicle can be easily achieved by varying several factors including, the consistency or rheology of the vehicle, BAS-loading, polymer molecular weight, hydrophilicity or hydrophobicity of the plasticizer, copolymer ratio, polymer to plasticizer ratio.

(*Shukla*, Col. 3, Line 57 to Col. 4, Line 4) (emphasis added).

The only teaching this paragraph makes relating to crystallinity is that biodegradable polymers may have varying crystallinity in addition to many other varying physical characteristics, such as physicochemical properties, hydrophilicity, hydrophobicity, molecular weight, amorphous states, and copolymer ratios. This provides no specific teaching to include a combination of an amorphous polymer and a crystallizable polymer.

The paragraph reproduced above states that it is the "consistency or rheology of the vehicle, BAS-loading, polymer molecular weight, hydrophilicity or hydrophobicity of the plasticizer, copolymer ratio, [and] polymer to plasticizer ratio" that determine the release of the BAS (biologically active substance). (*Shukla*, Col. 4, Lines 1-4). Again, the combination of an amorphous polymer with a crystallizable polymer, as specified in the present claims, is neither mentioned nor suggested. In fact, the passage from column 3 suggests that

whether a polymer is crystallizable or amorphous is irrelevant to release of the biologically active substance since they are excluded from the list of properties that *Shukla* indicates determine the release of the BAS.

The text relating to polymer crystallinity from column 9 and example 29 is reproduced below:

> For pulsatile or intermittent delivery of BAS such as vaccines, the biodegradable vehicle can be prepared with blends of **varying molecular weights of polymers or copolymers, or with blends of copolymers of varying copolymer ratios** (e.g. 50/50 PLGA and 85/15 PLGA or 100% PLA and 25/75 PLGA) or blends of different types of biodegradable polymers with **varying hydrophobicity or lipophilicity or crystallinity** (e.g. 1:1 of PLA:PCL or 1:3 of PLA:PCL or 1:1 of 50/50 PLGA:PCL).
>
> (*Shukla*, Col. 9, Lines 28-36) (emphasis added).

> For pulsatile or intermittent delivery of BAS such as vaccines, the biodegradable vehicle prepared with the methods described in examples 1-20 can be prepared with blends of **varying molecular weights of polymers or copolymers, or with blends of copolymers of varying copolymer ratios** such as 50/50 PLGA and 85/15 PLGA or 100% PLA and 25/75 PLGA, or blends of different types of biodegradable polymers with **varying hydrophobicity or lipophilicity or crystallinity** such as 1:1 of PLA:PCL or 1:3 of PLA:PCL or 1:1 of 50/50 PLGA:PCL.
>
> (*Shukla*, Example 29, Col. 19, Lines 34-44) (emphasis added)

The text in column 9 and in example 29 are nearly identical. In these passages, *Shukla* states that at least five physical properties may be varied to provide the biodegradable vehicle.[5] A nearly infinite number of possible

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[5] Example 29 is a prophetic Example written in the present tense. This Example is merely a suggestion of what may be possible. The Example fails to explain how this passage provides

combinations is proposed by *Shukla* in these passages: blends of varying molecular weights of polymers and copolymers are suggested, but no specific molecular weights are given, even in the five blends listed; randomness, order, or the presence of blocks, within the listed copolymers is not specified. Therefore this list includes nearly an infinite number of combinations. The disclosures of column 9 and example 29 fail to provide any specific teaching to select a combination of an amorphous polymer and a crystallizable polymer, as specified by Applicants' claim 1.

Considering the nearly infinite number of possible combinations of polymers and physical properties mentioned in columns 3, 9, and example 29 of *Shukla*, there would be no motivation for one of ordinary skill in the art to select a combination of a crystallizable polymer and an amorphous polymer, included in the claimed invention. (MPEP § 2131.02). Furthermore, because the agent release profiles of the present invention are very different from those of *Shukla*, one of ordinary skill in the art would not be motivated by the data and examples of *Shukla* to select from the many potential combinations suggested by *Shukla*, a combination of a crystallizable polymer and an amorphous polymer. (MPEP

---

guidance as to which polymers and which combinations of the many physical properties listed are relevant. Thus, even if *Shukla* were to specifically disclose a crystallizable polymer in combination with an amorphous polymer, which it does not; the reference fails to enable this combination and cannot anticipate claim 1. Akzo N.V. v. United States ITC, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986).

§ 2131.03). *Shukla* does not describe the present invention with sufficient specificity to anticipate the claims.

C. The Cited References Fail to Render Obvious Under 35 U.S.C. § 103 Claims Including the Combination of a Crystallizable Polymer and an Amorphous Polymer.

The Examiner has rejected claims 18 and 56 as obvious over *Shukla* alone or in combination with *Weisheng*. *Shukla* alone cannot render the invention of claims 18 or 56 obvious. Claims 18 and 56 specify that the amorphous polymer is poly (D,L-lactide). *Shukla* does not suggest the inclusion of poly (D,L-lactide) or that this specific polymer is amorphous and should be combined with a crystallizable polymer. Instead, and as stated by the Examiner, *Shukla* teaches that blends of two different polymers or copolymers (e.g. blends of polycaprolactone and polylactic acid or polycaprolactone and poly-lactic-co-glycolic acid) can result in a vehicles with varying degradation kinetics where the more hydrophilic or amorphous polymer may degrade at a much faster rate. (*Shukla*, Column 7, Lines 53-50). Such a generic teaching of polymer classes does not suggest inclusion of poly (D,L-lactide), as specified by claims 18 and 56. In fact, the Examiner admits that *Shukla* fails to disclose poly (D,L-lactide), stating that "*Shukla* does not exemplify instant poly(D,L-lactide)." (Paper No. 17, Page 6).

To make up for this deficiency in *Shukla*, the Examiner improperly combines it with *Weisheng*, which mentions racemic poly (D,L-lactic acid) in the context of an acceptable ingredient for chewing gum. Neither *Shukla* nor *Weisheng* provide any motivation to combine a crystallizable polymer with poly (D,L-lactide), a racemic polymer used in chewing gum. *Weisheng* teaches that crystallizable polymers are unsuitable for use in chewing gum, while amorphous polymers, such as poly (D,L-lactide), provide desirable chewing characteristics. *Shukla* provides no suggestion that would motivate one to select a polymer having desirable chewing characteristics. Likewise, there could be no expectation that a successful drug delivery implant would result from such a combination.

Even when combined as suggested by the Examiner, *Shukla* and *Weisheng* do not suggest the invention of claims 18 and 56. If poly (D,L-lactide) is selected as the "polylactic acid" to be used in combination with "polycaprolactone," as taught by *Shukla* in column 7, lines 45-46, a composition having two amorphous polymers results. This is not the claimed invention, which includes a crystallizable polymer.

The obviousness rejections over *Shukla* alone, and *Shukla* in combination with *Weisheng*, should be withdrawn. The Examiner has failed to provide a motivation to combine the references or a reasonable likelihood of success as required under In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) to

sustain an obvious rejection. (M.P.E.P. § 2143). Even the Examiner's combination and modification of *Shukla* and *Weisheng* fails to suggest inclusion of both an amorphous polymer and a crystallizable polymer.

The Examiner has also rejected claims 4, 8, 19, 50, 54, and 57 as obvious over *Shukla* with *Brodbeck* '200. *Brodbeck* '200 describes biodegradable compositions containing a single copolymer of D,L-lactide and glycolic acid. (*See* Examples 1, 2, and 8; Tables 1 and 2). A copolymer is a single polymer, not a mixture of polymers. Therefore, *Brodbeck* '200 provides no teaching that any of these polymers are crystallizable or amorphous, and no suggestion to combine crystallizable and amorphous polymers.

Shukla lacks the solvents and emulsifying agents specified by these claims, and therefore the Examiner attempts to supply them from *Brodbeck* '200. While these materials may be disclosed in *Brodbeck* '200, *Shukla* still fails to suggest a combination of a crystallizable polymer with an amorphous polymer. *Brodbeck* '200 does not cure this deficiency. Thus, the obviousness rejection with regard to claims 4, 8, 19, 50, 54, and 57 should be withdrawn.

The Examiner rejects claims 4, 7, 19, 53, and 57 as obvious over *McHugh*, *Brodbeck*, and *Graham* in view of *Brodbeck* '200. As addressed in Section A of this Argument, *McHugh*, *Brodbeck*, and *Graham* do not disclose crystallizable polymers. *Brodbeck* '200 also fails to disclose crystallizable polymers. Because *McHugh*, *Brodbeck*, *Graham*, and *Brodbeck* '200 fail to

disclose a crystallizable polymer, they cannot suggest inclusion of an amorphous polymer and a crystallizable polymer.

D. Data in the Application Demonstrates Unexpected and Surprising Results, Providing Further Evidence of the Unobviousness of the Claimed Invention.

Further evidence of unobviousness is provided by comparison of Examples 1-5 of the present application. Example 5 includes only a biodegradable amorphous polymer (PDLA), while Example 1 includes only a crystallizable polymer (PCL). Examples 2, 3, and 4 are various blends of crystallizable and amorphous polymers. These examples, and the associated Figures 5 and 10, illustrate the unexpected and surprising results of the claimed invention.

Both the release of the bioactive agent and the water absorption characteristics may be varied by controlling the amount of crystallizable polymer verses amorphous polymer in the compositions. For example, the presence of a crystallizable polymer may provide for a rapid release of the bioactive agent when crystallization occurs. The type and relative amount of crystallizable polymer may affect both the timing and the amplitude of the rapid release. There is nothing in the applied references to suggest these unexpected and surprising results, and therefore these results further demonstrate the unobviousness of the claimed invention.

E. The Claims are Independently Patentable

Independent claim 1 focuses on a composition for controlled release of a bioactive agent. The composition includes biodegradable crystallizable and amorphous polymers in addition to a biocompatible solvent and a bioactive agent. The Examiner was unable to find any art disclosing a composition for controlled release of a bioactive agent that included both a crystallizable polymer and an amorphous polymer.

Each of the claims depending from claim 1 provide additional limitations not found in the independent claim from which they depend. Depending from independent claim 1, claim 2 characterizes the miscibility of the solvent. Claim 3 adds an additional component solvent to the composition of claim 1. Claim 4 adds an emulsifying agent to the composition. Claim 5 provides for the sterility of the composition. The references cited by the Examiner fail to suggest any of these elements.

Depending from independent claim 1, claim 6 specifies that the biodegradable crystallizable polymer is a polyester. Claim 7 requires that the biodegradable crystallizable polymer is poly (ε-caprolactone). Claim 8 specifies that the biocompatible solvent is ethyl benzoate. Claim 17 depends from independent claim 1 and requires the biodegradable amorphous polymer to be a polyester. Claim 18 also depends from claim 1 and specifies that the biodegradable amorphous polymer is poly (D,L-lactide). Depending from claim

18, claim 19 requires that the biodegradable crystallizable polymer is poly (ε-caprolactone) and that the biocompatible solvent is ethyl benzoate. Claim 38 provides a method of making the composition of claim 1. Claim 58 requires that the composition of claim 1 have multiple layers. Again, the references cited by the Examiner fail to suggest any of these elements.

Claim 34 provides a method of administering a bioactive agent by inserting the composition of claim 1 into an organism. Claim 59 requires that the insertion is performed by injecting. Depending from claim 34, claim 48 characterizes the miscibility of the solvent. Claim 49 adds an additional component solvent to the composition that is inserted when the method of claim 34 is performed. Claim 50 adds an emulsifying agent to the composition of claim 34. Claim 51 provides for the sterility of the composition of claim 34. Again, the references cited by the Examiner fail to suggest any of these elements.

Depending from claim 34, claim 52 specifies that the biodegradable crystallizable polymer is a polyester. Claim 53 requires that the biodegradable crystallizable polymer is poly (ε-caprolactone). Claim 54 specifies that the biocompatible solvent is ethyl benzoate. Claim 55 depends from claim 34 and requires the biodegradable amorphous polymer to be a polyester. Claim 56 also depends from claim 34 and specifies that the biodegradable amorphous polymer is poly (D,L-lactide). Depending from claim 56, claim 57 requires that the biodegradable crystallizable polymer is poly (ε-caprolactone) and that the

biocompatible solvent is ethyl benzoate. Each invention is separate and independently patentable. Again, the references cited by the Examiner fail to suggest any of these elements.

IX. CONCLUSION

For the foregoing reasons, the claim rejections applied by the Examiner are unsustainable. Applicants respectfully request reversal of the Examiner's rejections.

Respectfully submitted,

Dated:

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X. APPENDICIES

APPENDIX A: PENDING CLAIMS

1. (Amended) A composition for controlled release of a bioactive agent, comprising:

a biodegradable crystallizable polymer;

a biodegradable amorphous polymer;

a biocompatible solvent; and

a bioactive agent.

2. (Original) The composition of claim 1, wherein the solvent has a miscibility with water less than 7 percent by weight.

3. (Original) The composition of claim 1, further comprising at least one biocompatible component solvent.

4. (Original) The composition of claim 1, further comprising an emulsifying agent.

5. (Original) The composition of claim 1, wherein the composition is sterile.

6. (Original) The composition of claim 1, wherein the biodegradable crystallizable polymer is a polyester.

7. (Original) The composition of claim 1, wherein the biodegradable crystallizable polymer is poly (ε-caprolactone).

8. (Original) The composition of claim 1, wherein the biocompatible solvent is ethyl benzoate.

Claim 9-16 (Cancelled)

17. (Original) The composition of claim 1, wherein the biodegradable amorphous polymer is a polyester.

18. (Original) The composition of claim 1, wherein the biodegradable amorphous polymer is poly (D,L-lactide).

19. (Original) The composition of claim 18, wherein the biodegradable crystallizable polymer is poly (ε-caprolactone) and the biocompatible solvent is ethyl benzoate.

Claims 20-33 (Cancelled)

34. (Amended) A method of administering a bioactive agent, comprising: inserting the composition of claim 1 into an organism,

wherein the composition comprises:

a biodegradable crystallizable polymer;

a biodegradable amorphous polymer;

a biocompatible solvent; and

a bioactive agent.

Claims 35-37 (Cancelled)

38. (Original) A method of making the composition of claim 1, comprising: combining ingredients;

wherein said ingredients comprise a biodegradable crystallizable polymer; a biocompatible solvent; and a bioactive agent.

Claims 39-47 (Cancelled)

48. (Previously Added) The method of claim 34, wherein the solvent has a miscibility with water less than 7 percent by weight.

49. (Previously Added) The method of claim 34, further comprising at least one biocompatible component solvent.

50. (Previously Added) The method of claim 34, further comprising an emulsifying agent.

51. (Previously Added) The method of claim 34, wherein the composition is sterile.

52. (Previously Added) The method of claim 34, wherein the biodegradable crystallizable polymer is a polyester.

53. (Previously Added) The method of claim 34, wherein the biodegradable crystallizable polymer is poly (ε-caprolactone).

54. (Previously Added) The method of claim 34, wherein the biocompatible solvent is ethyl benzoate.

55. (Previously Added) The method of claim 34, wherein the biodegradable amorphous polymer is a polyester.

56. (Previously Added) The method of claim 34, wherein the biodegradable amorphous polymer is poly (D,L-lactide).

57. (Previously Added) The method of claim 56, wherein the biodegradable crystallizable polymer is poly (ε-caprolactone) and the biocompatible solvent is ethyl benzoate.

58. (Previously Added) The composition of claim 1, wherein the composition is multi-layered.

59. (Previously Added) The method of claim 34, wherein inserting is by injecting.

APPENDIX B: DOCUMENTATION ON POLY(D,L-LACTIDE-CO-GLYCOLIDE)

DOCUMENTATION

on

Poly(D,L-lactide-co-glycolide) 50:50

RESOMER® RG 50x

According to Directive 75/318 EEC

This Applicants Part on the Drug Master File supersedes the file dated September 14, 1992

Boehringer Ingelheim KG
BU Special Products
P.O. Box 200
D-55216 Ingelheim/Rhein
GERMANY

Table of content

NAME AND SITE OF MANUFACTURER

Administrative

Boehringer Ingelheim KG
Business Unit Special Products
P.O. Box 200
D-55216 Ingelheim, Germany

Manufacturing Facility

Same as above

Responsible Official

Dr. Hans-Bernd Amecke
General Manager
Boehringer Ingelheim KG
BU Special Products
P.O. Box 200
D-55216 Ingelheim, Germany

C.1.1. SPECIFICATION AND ROUTINE TESTS

Specification of RESOMER® RG 50x:

Description

White to brownish substance

Odour

Odourless or almost odourless

Identification, NMR spectrum

The ^{1}H NMR spectrum of the test substance should correspond to the spectrum obtained from a RESOMER RG 50X (H) reference substance.

Polymer composition, NMR spectrum

The ratio of D,L-lactide units to glycolide units in the copolymer should fall into the range of 48:52 to 52:48 mole %.

Residual monomer content, gas chromatography

D,L-Lactide monomer:	Not more than 0.5 % (w/w)
Glycolide monomer:	Not more than 0.5 % (w/w)

Residual solvents, head space gas chromatography

Acetone:	Not more than 0.1 %

Heavy metals, USP XXIII

Not more than 10 ppm

Tin, atomic absorption spectroscopy (AAS)

Not more than 100 ppm (standard series)
Not more than 200 ppm (H series)

Water content, Karl-Fischer titration

Not more than 0.5 %

Sulphated ash, Method: USP XXIII

Not more than 0.1 %

Inherent viscosity, Method: viscosimetry of a diluted polymer solution

RESOMER® RG502	0,16 - 0,24 dl/g
RESOMER® RG502 H	0,16 - 0,24 dl/g
RESOMER® RG503	0,32 - 0,44 dl/g
RESOMER® RG503 H	0,32 - 0,44 dl/g
RESOMER® RG504	0,45 - 0,60 dl/g
RESOMER® RG504 H	0,45 - 0,60 dl/g
RESOMER® RG505	0,61 - 0,74 dl/g
RESOMER® RG505 H	0,61 - 0,74 dl/g
RESOMER® RG506	0,75 - 0,95 dl/g
RESOMER® RG506 H	0,75 - 0,95 dl/g

The analytical methods used are enclosed as Appendix 1:
"Testing Specifications for Poly(D,L-lactide-co-glycolide) 50:50

C.1.2.1. NOMENCLATURE

1.2.1.1 International non-proprietary name (INN)

None

1.2.1.2 United States adopted name

None

1.2.1.3 Chemical name

Poly(D,L-lactide-co-glycolide) 50:50 (mol%)

1.2.1.4 Other names

RESOMER® RG 50x (H)

(x depends on the inherent viscosity ≈ molecular weight, H denotes the hydrophilic type of polymer)

1.2.1.4 Laboratory code

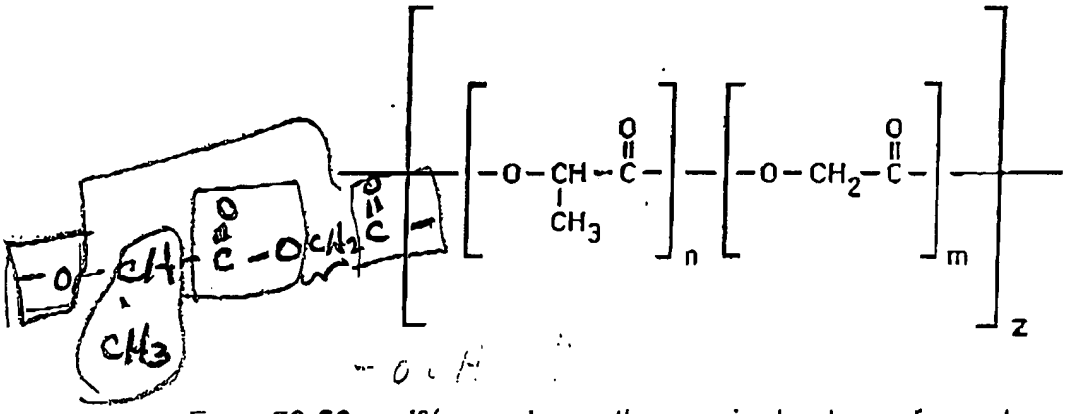
None

C.1.2.2. DESCRIPTION

1.2.2.1 Physical form

White to brownish powdery substance

1.2.2.2 Structural formula



For a 50:50 mol% copolymer the nominal values of n and m are 1, the value of z depends on the molecular weight average.

1.2.2.3 Molecular formula

$[(C_3H_4O_2)(C_2H_2O_2)]_z$

1.2.2.4 Molecular weight

A synthetic polymer is a mixture of molecules of different molecular weights, build up by combining different amounts of monomer units. Therefore a polymer can be characterised only by its molecular weight **average**. For linear, unbranched and not cross linked polymers like the polyester poly(D,L-lactide-co-glycolide) 50:50 there is a relationship between the relative viscosity *(viscosity ratio)* of a diluted polymer solution

$$\eta_{rel} = \frac{t_{solution}}{t_{solvent}} \qquad t = \text{flow time}$$

and the molecular weight. Commonly the inherent viscosity *(logarithmic viscosity number)*

$$\eta_{inh} = \frac{\ln(\eta_{rel})}{c}$$

is used to characterise the molecular weight average of a polymer.
A molecular weight average can be calculated, if the parameters K and α of the so called Mark-Houwink equation (MHE) are known:

$$[\eta] = K \cdot M_{vis}^{\alpha}$$

or transformed

$$M_{vis} = ([\eta] / K)^{1/\alpha}$$

The intrinsic viscosity *(limiting viscosity number)* $[\eta]$ can be determined in a dilution series

$$[\eta] = \lim_{c \to 0} \eta_{red} = \lim_{c \to 0} \eta_{inh}$$

or out of single point measurements by e.g. the Solomon-Ciuta-Approximation

$$[\eta] = \frac{\sqrt{2(\eta_{spec} - \ln \eta_{rel})}}{c}$$

The calculated viscosity average is nearly equal to the most importend weight average of the molecular weight.
So far no reliable MHE parameters are known for the poly(D,L-lactide-co-glycolides), therefore the molecular weight is assessed in terms of inherent viscosity.

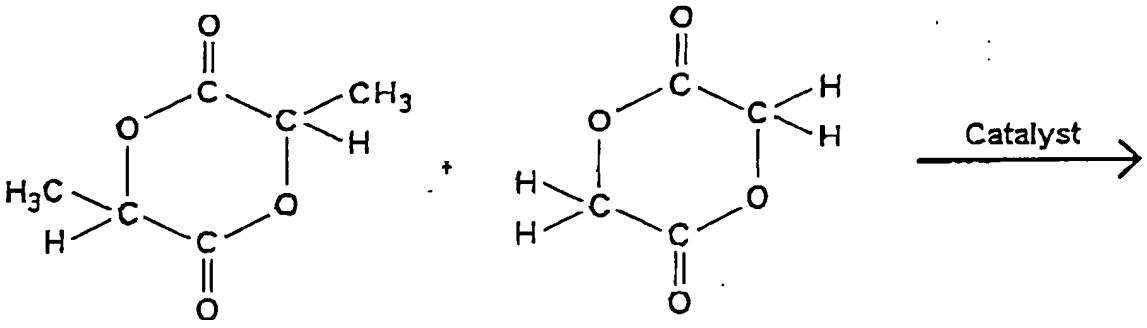
C.1.2.3 MANUFACTURING PROCESS

1.2.3.1 Name and Address of the Manufacturing source

Boehringer Ingelheim KG
Business Unit Special Products
P.O. Box 200
D-55216 Ingelheim, Germany

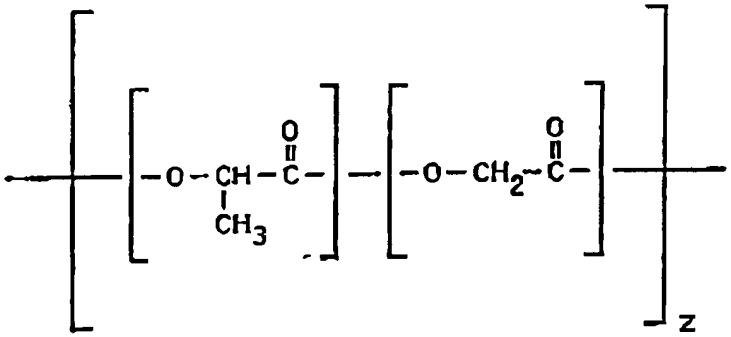
1.2.3.2 Flow Diagram of the Manufacturing Process

Step 1: Polymerisation



D,L-Lactide (I)
$C_6H_6O_4$

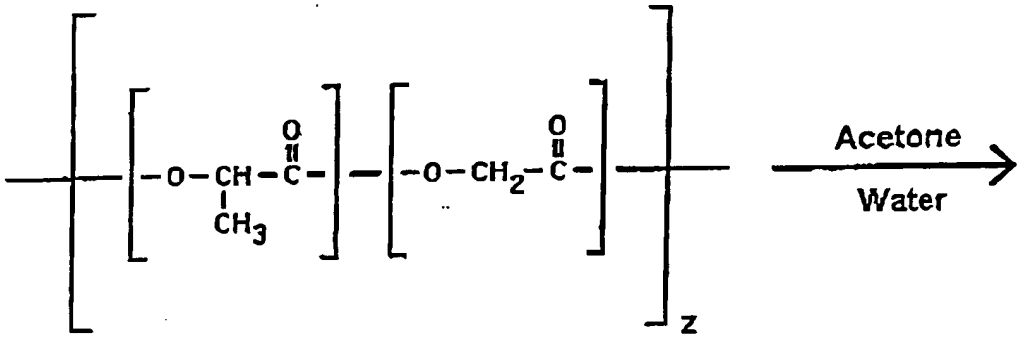
Glycolide (II)
$C_4H_4O_4$



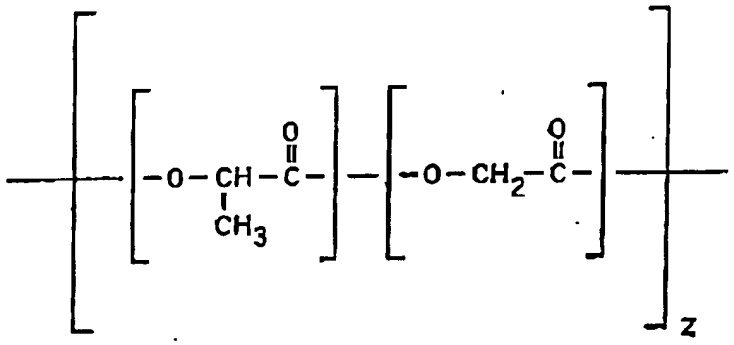
III

Poly(D,L-lactide-co-glycolide) 50:50, crude copolymer
$[(C_3H_4O_2)(C_2H_2O_2)]_z$

Step 2: Purification



III
Poly(D,L-lactide-co-glycolide) 50:50, crude copolymer
$[(C_3H_4O_2)(C_2H_2O_2)]_z$



IV
Poly(D,L-lactide-co-glycolide) 50:50, purified copolymer
$[(C_3H_4O_2)(C_2H_2O_2)]_z$

The nominal values of z depends on the molecular weight average of a given copolymer.

Hereby is stated that Poly-(D,L-lactide-co-glycolide) 50:50 will not be released for further processing or shipment unless all requirements of the valid testing specification are met.

1.2.3.3 Materials used

The following materials are used to produce poly(D,L-lactide-co-glycolide) 50:50:

Reagents:	D,L-lactide S Glycolide S
Catalyst:	Stannous(II)-2-ethylhexanoate (Okstan II)
Last Solvents:	Acetone Water

C.1.2.5 CHEMICAL DEVELOPMENT OF PRODUCT

1.2.5.1 Evidence of chemical structure

The lactide and glycolide units of the polymer can be identified by proton NMR spectroscopy. The signals of the polymers can be clearly differentiated from those of the corresponding monomers.

1.2.5.2 Potential isomerism

Poly(D,L-lactide-co-glycolide) 50:50 is an intrinsically amorphous (glassy) polymer. Therefore no crystallinity and hence no different crystal structures can occur.
It is known from the polymerisation of the pure homopolymers poly(L-lactide) and poly(D,L-lactide) and proven by the measurement of the optical rotation, that no racemization of the optical centre of the lactide unit occurs during the polymerisation reaction.

1.2.5.3 Physico-chemical characterisation

The molecular weight average of the polymer is characterised by measuring the inherent viscosity
As an intrinsically amorphous polymer poly(D,L-lactide-co-glycolide) 50:50 has no melting point or range. In a thermal analysis such as DSC (differential scanning calorimetry) typically only a glass transition, T_g, can be detected.

1.2.5.4 Analytical development

Identity and copolymer composition is checked by proton NMR. At least a 250 MHz spectrometer should be applied to resolve the monomer/polymer peaks.

Residual monomers are determined by a standard gas chromatography method, using a packed column system.

Residual solvents are determined by standard head space gas chromatography.

To determine heavy metals and sulphated ash, Pharm. Eur. and USP XXIII methods are applied.

The amount of residual tin is measured by atomic absorption spectroscopy (AAS).

Water is determined by classical Karl-Fischer titration.

To determine the inherent viscosity chloroform is used as solvent at 25 °C. The concentration is always 0.1 g/dl (=0.1 % solution). An Ubbelohde type of viscometer is used.
The method is based on national and international standards (ISO 1628/1 , DIN 53012, DIN 51562).

The testing specifications for RESOMER® RG 50x are enclosed as Appendix 1 to this documentation.